REVIEW

Pathophysiology and Treatment of Diabetic Neuropathy

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The scope of the present review is to describe epidemiology, classification, symptomatology and treatment of diabetic peripheral somatic neuropathy and autonomic neuropathy. Special attention is paid to the use of local anaesthetic agents in painful diabetic neuropathy. Denervation hypersensitivity is a characteristic of autonomic neuropathy in diabetic patients. The pathophysiology behind this phenomenon is elucidated in this review and most recent studies related to diabetic encephalopathy are reviewed. References for this review were acquired via a MedLine and MedLars literature search. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Neuropathy is among the most frequent and disabling complication of diabetes mellitus, with diabetic neuropathy being the most common form of neuropathy in the western world. It remains the most insidious, least understood, assessed, detected, and most difficult to treat of all the late diabetic complications. Symptoms of neuropathy were already mentioned by Areatus in his classical description of diabetes from approximately 50 AD.[1] The first clinical description of diabetic neuropathy is however attributed to Rollo, who described a patient with 'pain and paraesthesia'.[2] The syndrome was described in more detail during the last century, but it was not until 1945 that the first comprehensive description of this disorder was published.[3] Since then considerable knowledge has been gained about the epidemiology, pathogenesis, pathophysiology and treatment of this complication of diabetes. Disabling symptoms like chronic pain, foot ulcers, orthostasis and impotence are frequent findings in patients with neuropathy. Furthermore, patients with autonomic neuropathy are characterized by maladaptation to everyday situations like exercise and hypoglycaemia and autonomic dysfunction is related to increased risk of death.[4,5]

The pathogenesis of diabetic neuropathy, as for other late diabetic complications, is not fully understood. Metabolic factors, vascular abnormalities and other mechanisms are proposed. The metabolic hypothesis is substantiated by the fact that glycaemic control influences the onset and progression of diabetic neuropathy, as shown in the Diabetes Control and Complications Trial[6] and other long-term trials of strict metabolic control.[7–10] In nerve, eye and kidney tissue, where glucose is transported independently of insulin, hyperglycaemia induces a high intracellular glucose concentration. The hexokinase pathway is thereby saturated, resulting in glucose being metabolized by the polyol pathway and converted to sorbitol by aldose reductase. Sorbitol is thereafter converted to fructose by sorbitol dehydrogenase.[11,12] Accordingly, hyperglycaemia will lead to accumulation of sorbitol and fructose in nerve tissue. Animal studies have shown that endoneural myoinositol and phosphoinositides are depleted and sodium potassium adenosine triphosphate ATP-ase and protein kinase C are reduced. Furthermore, intermediate metabolites are changed, cytosolic redox potential is reduced due to an increased NADH/NAD ratio, metabolism of free fatty acid is impaired, and axonal transport of proteins is reduced.[13–17] These biochemical abnormalities lead to structural abnormalities and functional loss in the nerve tissue.

Glycosylation of proteins as a consequence of hyperglycaemia also leads to the formation of (reversible) Amadori products and irreversible advanced glycosylated endproducts (AGE) on especially 'long-lived' proteins, such as myelin. The consequence of this glycosylation is further impairment of nerve function.[18–22]

In diabetic neuropathy, epineural and endoneural microangiopathy with endothelial cell hyperplasia and basement membrane thickening have been demonstrated.

Abbreviations: AGE advanced glycasylated endproducts, DAN diabetic autonomic neuropathy, DCCT diabetes control and complication trial, ARI aldose reductase inhibitor, VAS visual analogue scale, FIS five item symptom score, HRV heart rate variation, QSART quantitative sudomtor axon reflex test, DHPG dihydorroxyphenylglycol, VPT vibration perception threshold, PNS peripheral nervous system, CNS central nervous system, EEG electroencephalograms, VER visual evoked response, ABR auditory brain response, MRS magnetic resonance scanning

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These changes, together with arteriovenous shunting and haemorheological abnormalities, may lead to reduced endoneural blood flow. The vascular hypothesis suggests that this reduction in endoneural blood flow leads to ischaemia, hypoxia, oxidative stress, and functional loss of nerve tissue.[23] Indeed, patients with chronic obstructive airways disease develop peripheral neuropathy with similar microvascular changes as seen in diabetic neuropathy.

Other pathogenetic factors implicated in diabetic nerve damage include deprivation of growth factors such as nerve growth factors, although their specific involvement is not yet fully understood.[24,25] Immunological mechanisms have been proposed in the aetiology of autonomic neuropathy. This is based on the finding of a clinical association with iritis,[26] increased levels of circulating immune complement breakdown products and activated T-lymphocytes,[27] and the detection of complement fixing antibodies to nervous tissue structures in patients with diabetic autonomic neuropathy (DAN).[28] Furthermore, inflammatory infiltrates with lymphocytes and macrophages have been demonstrated but autoantibodies against sympathetic ganglia are not increased in long-term diabetic patients[29] or in autonomic nerves in patients with DAN.[30] However, whether these are coincident findings or if they play a pathogenetic role can only be ascertained from large scale prospective trials which are not available at present.

It seems reasonable to attempt to link this evidence into an unifying hypothesis that metabolic changes due to hyperglycaemia-induced increments in polyol pathway activity and formation of advanced glycosylated endproducts together induce nerve tissue damage and capillary endothelial thickening. Reduced blood flow, possibly accompanied by nerve growth factor depletion and autoimmunity, further accelerates functional loss.[21,31,32] The present review focuses on aspects of the pathophysiology and treatment of peripheral somatic and autonomic neuropathy and the existence of central neuropathy in patients with diabetes mellitus.

Peripheral Somatic Neuropathy

Classification

One of the major problems in research into diabetic neuropathy and its clinical impact has been the lack of a consistent and global classification of somatic peripheral diabetic neuropathy.[33–35] This is mainly due to the lack of knowledge of the pathogenesis, pathophysiology and the complex clinical presentation of the disease. Diabetic neuropathy can be divided into two major entities, clinical and subclinical neuropathy. Clinical neuropathy is characterized by the presence of clinically detectable signs and symptoms of neuropathy not attributable to other disease processes. Subclinical neuropathy implies abnormalities of nerve function based on functional testing, without concomitant clinical signs and symptoms of peripheral nerve disease. Based on clinical presentation and neuroanatomy, somatic neuropathy can be subdivided further into symmetrical polyneuropathy with involvement of several nerve trunks and focal neuropathy. Symmetrical polyneuropathy is divided further into sensory, motor (often proximal) or mixed sensorimotor neuropathy, which often coexists with autonomic neuropathy (Table 1). The symmetrical polyneuropathy with mixed sensorimotor involvement is the most common, accounting for approximately 80% of neuropathy in diabetic patients.

Focal neuropathy is subdivided into mononeuropathy (cranial neuropathy, radiculopathy (intercostal neuropathy)) or multifocal neuropathy (asymmetric proximal lower limb motor neuropathy—diabetic amyotrophy),[36,37] which are all comparatively rare (Table 1).

Epidemiology

Estimates of the incidence, prevalence, occurrence by age and sex, and the types of peripheral neuropathy encountered in different patient groups differ considerably in available surveys. The conflicting data currently available are a consequence of the lack of a consensus on basic definitions and classifications and differences in patient selection and diagnostic procedures. Accordingly, prevalence rates vary between 10 and 100%.[38–40] subclinical neuropathy being much more common than clinical neuropathy with a prevalence rate of between 50 and 100%.[37,41] The studies reporting 100% prevalence rates have all been based on nerve conduction studies. In the classical prospective study of 4400 diabetic patients by Pirart,[42] 50% had objective signs of neuropathy defined as abnormal reflexes and vibratory sensation after 25 years of diabetes. The Rochester neuropathy study had a prevalence rate for diabetic neuropathy of 50%, with 15% having clinical neuropathy.[43] During screening of a large diabetic clinic, 11% of insulin-treated patients were found to have signs and symptoms of neuropathy.[44] In a cross-sectional study of more than 6400 hospital-based diabetic patients, a prevalence rate of clinical neuropathy—based on a disability and symptom score—of 29% was found.[45] In this study, a positive correlation with age, duration of diabetes, and Type 2 diabetes was found. This is substantiated by others.[46] Furthermore, poor metabolic control, height and alcohol abuse are also correlated with the presence of diabetic neuropathy.[47,48]

Signs and Symptoms

Somatic diabetic neuropathy is characterized by a complex clinical picture depending on the type of neuropathy and the specific nerves affected. Dys-, para-, hypo- or hyperaesthesia, allodynia, burning, tingling, 'pins and needles' or 'electric shock-like- sensations, superficial or deep pain, muscle weakness or cramps are among the most commonly reported symptoms. Pain

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Table 1. Classification of diabetic neuropathies

Somatic neuropathy	Polyneuropathy	Sensory Motor Sensorimotor
	Focal neuropathy	Mononeuropathy (cranial, trunk and limb neuropathy) Multifocal neuropathy (diabetic amytrophy)
Autonomic neuropathy	Structural Functional	Subdivided according to: 1. ± Clinical symptoms 2. Subdivision of autonomic nervous system 3. organ systems involved
Central neuropathy	Clinical Subclinical	

is usually divided into a cutaneous dysaesthetic pain and a more deep nerve trunk pain, the first being characterized by burning and tingling, whereas the last is more aching and knife-like. The mechanism of pain in diabetic neuropathy is not known, but several have been proposed. One suggestion is that there is increased firing of abnormally excitable nociceptive fibres, particularly sprouting regenerating small myelinated A delta and/or unmyelinated C-fibres, and/or ectopic impulse generation with ephaptic transmission which relates to electrical cross talk between damaged nociceptive afferents and perhaps sympathetic nerves.[49] Central changes can follow peripheral nerve damage as dorsal root ganglion cells can spontaneously generate impulses when peripheral nerves are damaged. Other potential mechanisms could be loss of segmental inhibition of large myelinated fibres and small unmyelinated C-fibres, enhanced firing to physiological stimulation of nociceptive fibres in the nervi nervorum or ischaemia in the nervi nervorum.[50] Arteriovenous shunting that occurs in small nerve fibre disease involving the autonomic nerve system may also be a source of pain. Hyperglycaemia or rapid fluxes in plasma glucose may play a role in decreasing the threshold level for pain.[51] Symptoms are often aggravated during the night, when the patient is at rest.

Nerve biopsies are characterized by fibre loss and atrophy of both myelinated and unmyelinated fibres, degeneration and regeneration of fibres, and specific fibre lesions such as axo-glial dysjunction, swelling of the node of Ranvier, perinodal demyelination followed by remyelination, and microvascular abnormalities.[52] The small C-fibres seem to be more susceptible to damage than the large fibres and dysfunction of these small C-fibres is a typical early sign of neuropathy.[53]

Treatment

There are two different approaches that can be taken in the treatment of somatic diabetic neuropathy, either a primary or a secondary intervention strategy.

Primary Intervention

Primary intervention studies have been performed in rodents where aldose reductase inhibition has been shown to be efficacious.[54] Primary intervention trials in human diabetic neuropathy are few. The UK Prospective Diabetes Study and recently started studies with aldose reductase inhibitors are addressing primary intervention but no results are available at the present time. The only published study on primary prevention in man is the DCCT.[6] In this study 726 insulin-dependent diabetic patients without signs or symptoms of diabetic complications were allocated to either intensified or conventional blood glucose control. Neuropathy was defined as an abnormal neurological examination, consistent with peripheral sensorimotor neuropathy, plus either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic nerve function. After a mean duration of 5 years, intensified treatment (mean blood glucose 8.6 mmol l^{-1}) reduced the risk of developing neuropathy by 69 % compared to conventional treatment (mean blood glucose 12.8 mmol l^{-1}). Even though this study demonstrates that the degree of metabolic control strongly influences the development of neuropathy it is noteworthy that despite near-normal blood glucose control over 5 years 8% still developed abnormal clinical neurological signs and findings with 18% having developed abnormal nerve conduction tests.

Secondary Intervention

Metabolic Control. Many studies have been performed to test the hypothesis that improved metabolic control reduces the progression of existing diabetic complications and even ameliorates present abnormalities and symptoms. This has been addressed in long-term trials of strict metabolic control,[6–10] studies, in patients with pancreatic transplantation,[55] and in short-term trials of strict metabolic control.[56] Most of these studies have demonstrated a beneficial effect on nerve conduction velocities and symptomatology of peripheral diabetic neuropathy. In the DCCT, intensive therapy reduced the progression of existing neuropathy at 5 years by 57% compared to conventional treatment. Acute improvement of metabolic

control likewise can be effective in painful diabetic neuropathy.[57]

Aldose Reductase Inhibition. Based on the assumption that aldose reductase plays a central role in the development of late diabetic complications, several inhibitors of this enzyme have been clinically tested, mainly in secondary intervention trials. According to their chemical structure these inhibitors can be categorized into four subgroups, i.e. carboxylic acids, hydantoins, flavonoids, and other compounds.[58] Hydantoins have been shown to be toxic and are therefore no longer used. Initial studies in patients with diabetic neuropathy showed only minor benefits in the aldose reductase inhibitor (ARI) treated patients with minor improvement in nerve conduction velocity and either none or only minimal improvement in symptomatology.[59–63] Subsequent studies with more potent ARIs and better defined patient groups, longer treatment periods and improved study design have shown a more promising effect on neurophysiology and symptomatology.[64,67]

A beneficial effect of ARIs has likewise been demonstrated on nerve biochemistry and morphometry.[68,69] It seems that treatment has to be started rather early in the process of the disease before irreversible structural and functional changes have developed.[70,71] In order to improve further the effect of ARIs more potent compounds with higher nerve tissue receptor affinity and less toxicity need to be developed. At present the role of ARIs in the treatment and prevention of diabetic neuropathy and other late diabetic complications has not been established.

Symptomatic Intervention

Many agents have been tested in the treatment of pain due to diabetic neuropathy. Patients with mild symptoms will often benefit from mild analgesic agents.[72] In more severe cases, the tricyclic antidepressants (imipramine, amitriptyline, and nortriptyline)[73] given alone or in combination with fluphenazine[74] have demonstrated an effect in double-blind controlled trials. Their effectiveness, which is independent of their antidepressive effect,[75] could be due either to the inhibition of noradrenaline and serotonin neuronal re-uptake as suggested by Sindrup[76] and/or a direct effect on opioid receptors. The serotonin re-uptake inhibitors,[77] carbamazepine,[78] gamma-linolenic acid,[79] topical capsacain,[80] and alpha-lipoic acid[81] have likewise been demonstrated to be effective. Drugs like gangliosides, phenytoin, cyano-cobolamin (vit B12), and dietary supplemention with myoinositol have not shown convincing effects. Opiates are generally not very effective[82] and are rarely used, also because of their addicting properties.

Studies with Lignocaine and Mexiletine

In a double-blind placebo controlled cross-over study lignocaine was shown to be effective in a single intravenous dose of 5 mg kg^{-1} body weight in patients with painful diabetic neuropathy.[83] Mexiletine, the oral analogue of lignocaine, at a dose of 10 mg kg^{-1} body weight in a double-blind randomized placebo controlled study of 26 weeks duration, improved symptoms but not signs in patients with chronic painful diabetic neuropathy.[84] Patients included in both these studies were Type 1 or Type 2 diabetic patients with painful diabetic neuropathy of more than 6 months duration. They had more than one of the following symptoms: pain, dysaesthesia, paraesthesia, nightly exacerbation of symptoms or sleep disturbances. During the studies these five symptoms were assessed in the outpatient clinic with a five-item symptom score (FIS-score), with each graded as not present, mild, moderate or severe.

Patients recorded their symptoms before and during the study on a visual analogue scale (VAS) and neurological examination included tests for reflexes, sensation (touch, temperature, pain), joint position sense, motor function and autonomic function with beat to beat variation and postural blood pressure fall. Both lignocaine and mexiletine relieved symptoms (VAS, FIS-score) but had no effect on any of the objective tests. These results could not be explained by a change in metabolic control as assessed by HbA_{1C}. Other studies have subsequently confirmed these observations.[85–91] In one study,[88] three different doses of mexiletine were tested, i.e. 225 mg day^{-1}, 450 mg day^{-1} and 675 mg day^{-1}. The study did not show any further improvement when raising the dose above 450 mg day^{-1}. Accordingly, the optimal dose for the treatment of painful diabetic neuropathy is lower than that recommended for its antiarrythmic activity (600–800 mg day^{-1}). This is important as a number of side-effects of mexiletine are dose-dependent and Stracke and co-workers reported that the frequency of adverse events rose from 2.4 to 33.3% when increasing the dose from 450 to 675 mg/day.[88] In our study with 10 mg kg^{-1} bodyweight, mild adverse events (nausea, hiccough, and tremor) developed in 3 out of 16 patients (19%). We could not show any correlation between effect (measured by FIS-score) and plasma concentration of mexiletine taken fasting at visits to the outpatient clinic. Neither could we demonstrate a threshold plasma concentration for effect. This problem was specifically addressed in one study[91] in which it was suggested that intravenous lignocaine gave an analgesic response in patients with neuropathic pain which was characterized by a threshold value and not an ordinary dose–response. The authors found a relief of pain over a narrow dose and plasma concentration range.

The mechanism of action of the observed symptomatic effect is uncertain. Both peripheral and central mechanisms are proposed.(92 The capacity of mexiletine to block sodium channels and thereby inhibit the hyperexcitable spontaneous firing in regenerating myelinated and unmyelinated fibres characteristic of painful diabetic neuropathy could explain the findings.[93] We have demonstrated that lignocaine administration results in an increase in the nociceptive flexor reflex threshold indicating an effect at the spinal or supraspinal level.[94] This is in accordance with other investigators[95,96] and the fact that we could

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not show any effect on the clinical stigmata of neuropathy in any of our studies. Neither could we demonstrate any effect of lignocaine on the cerebral blood flow in patients with painful neuropathy,[97] indicating that the effect is not vascular. However, we have found an increase in plasma levels of the endogenous opioid peptides beta-endorphin and dynorphin after infusion of lignocaine in such patients.[98] This effect could contribute to the pain relieving effect of lignocaine and mexiletine. Mexiletine seems to be a well-tolerated and effective alternative in the treatment of painful diabetic neuropathy.

In the treatment of diabetic patients with painful neuropathy, it can be concluded that it is important to optimize metabolic control with more intensified treatment regimens. As regards pharmacologic intervention, simple analgesics should be tried first. Tricyclic antidepressants such as imipramine should be the next drug of choice and, if required, combined with fluphenazine. Mexiletine, carbamazepine and serotonin re-uptake inhibitors should then be tried in this order. Diazepam is the drug of choice in patients with cramps.[99] In many patients physiotherapy will further improve the condition.

Autonomic Neuropathy

Diabetic autonomic neuropathy (DAN) is the most common cause of autonomic failure. Symptomatic autonomic neuropathy is, however, rare and present in less than 5 % of diabetic patients. There is only a weak correlation between abnormal autonomic cardiovascular tests and the presence of symptoms. This is partly explained by the lack of specificity of the tests used and the complexity of symptoms. As autonomic nerves are small fibre nerves, defects appear early in the evolution of diabetic neuropathy.[100]

The autonomic nervous system (ANS) is usually regarded as an efferent system to a variety of organs such as eyes, heart, gastrointestinal tract, respiratory tract, genitourinary tract, vessel wall and endocrine glands. Yet, afferent sensory autonomic axons responsible for vital regulatory functions do exist. Accordingly dysfunction of the ANS will give rise to a variety of subclinical or clinical defects. These include postural hypotension, vasomotor instability, gastroparesis, diarrhoea, constipation, respiratory dysfunction, neuroendocrine abnormalities, impotence, urinary bladder dysfunction, defects in temperature regulation and maladaptation to exercise. The increased mortality described in DAN is partly linked to the long QT syndrome with ventricular arrhythmias, silent ischaemia, cardiac arrest, and sudden death often without cardiovascular symptoms. Additionally it has been proposed that respiratory malfunction contributes to a poor prognosis.[101–103,104]

Based on this variety of manifestations, there have been several suggestions for the classification of DAN. Recently the American Diabetes Association and the American Academy of Neurology published a consensus report on standardized measures in diabetic neuropathy (see Part 1, Consensus Report[35]). They propose a classification into a structural (with structural lesions of the neuron) or functional type with further subdivision based on the overt or subclinical nature of the disorder, the specific subdivisions of the autonomic nervous system and the specific organ systems involved. The subclinical type is only diagnosed by tests and the clinical type presents itself with signs and symptoms (Table 2).

Epidemiology of DAN

The problems encountered in epidemiological studies of somatic diabetic neuropathy are accentuated with DAN, especially as it involves an even greater spectrum of clinical entities and there is no consensus over criteria for its diagnosis at present. DAN is much more widespread with an earlier onset than originally estimated but seldom causes symptoms. In a study of newly diagnosed Type 1 diabetic patients, 16.8 % were found to have DAN based on spectral tests combined with standard analysis of heart rate variation (HRV).[105] Accordingly DAN is present early in the course of diabetes, reflecting involvement of small nerve fibres. In a group of 1171 consecutive Type 1 and Type 2 diabetic patients, six sensitive tests of HRV were performed and in 34 % of Type 1 and 25 % of Type 2 diabetic patients at least two tests were abnormal.[106] In a study of 506 insulin-treated patients, 17 % had abnormal function defined by at least 2 out of 4 abnormal cardiovascular tests.[107] This is in agreement with a reported prevalence rate of 16 % in a population-based study.[108]

The majority of patients who develop signs of DAN do not become symptomatic.[109] The presence of DAN correlates with somatic neuropathy, nephropathy, retinopathy, age, and duration of diabetes[106] and it may well be a prerequisite in the development of foot ulcers.[110] Mortality is increased in patients with symptomatic DAN. In a 10-year follow-up study, the mortality rate was 37 %[111]—somewhat lower than the 50 % found in a subsequent 5-year follow-up study by Ewing.[4] In another 5-year study the mortality rate was found to be 27 % compared to 5 % in those with normal autonomic function.[112] The influence of asymptomatic autonomic failure to mortality is not known.

Autonomic Function Test

A number of tests for autonomic dysfunction have been described. They can be classified as cardiovascular, biochemical or microneurographic.[103,113,114] Cardiovascular tests are the most widely used. Several stimuli influence heart rate and, by standardizing these, it is possible to determine the presence or absence of autonomic dysfunction. Cardiovascular test-stimuli that are used to establish a diagnosis of DAN involve:

1. Deep breathing (6 breaths min^{-1}) in a supine or sitting position (i.e. beat to beat (RR) variation).

Table 2. Quantitative tests for neural function in diabetic neuropathy

	Pathway	Test
Somatic	Dorsal columns	Vibration perception threshold
		Proprioception
		Light touch
	Spinothalamic	Thermal perception testing
		Pain threshold testing
		Cutaneous current perception
Autonomic	Parasympathetic	Resting heart rate
		Beat to beat (RR) variation
		Valsalva manoeuvre
		30/15 Ratio
	Sympathetic	QSART
		Blood pressure response to standing
		Pupil size
	Both	Plasma norepinephrine (supine, standing up)
		HR variation (time domain, frequency domain analysis)

2. Standing, where the ratio in pulse rate at 15 s (normally tachycardia) and 30 s (normally bradycardia) after standing up is measured, i.e. the 30/15 ratio.
3. Valsalva manoeuvre, involving forced expiration for 15 s and measurement of the longest RR/shortest RR interval before, during and after. This latter test is not advocated in patients with proliferative diabetic retinopathy.

Other cardiovascular tests that are less specific and not validated include stimuli with mental arithmetic stress and coughing. Another approach is to measure background heart rate (HR) variation either using a time–domain method or a frequency–domain method using spectral analysis.[115] These tests have not, however, been validated in large-scale investigations. Other cardiovascular tests reflect the impact of blood pressure of a given stimulus such as standing up or sustained exercise using a handgrip dynamometer. Neurophysiological tests include (Table 2):

1. quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, and other sudomotor tests;
2. salivation test;
3. blood flow after cold immersion;
4. dark adapted pupil size after parasympathetic blockade.[116]

The recommendation from the ADA consensus report[35] is to use the following: beat to beat variation (parasympathetic), Valsalva manoeuvre (parasympathetic), postural blood pressure (sympathetic), QSART (sympathetic), and the dark adapted pupil size after total parasympathetic blockade (sympathetic).

The most commonly used biochemical test is the measurement of noradrenaline in the supine position and/or stimulated after standing (Table 2). Supine values are used as an index to differentiate between pre- and postganglionic lesions. With preganglionic lesions the supine value is within the normal range, the response to standing is decreased. In the presence of postganglionic lesions (if widespread) both values are decreased. Normally both are reduced in DAN, but the supine noradrenaline concentration has been reported to be within normal range.[117] There are some inherent problems related to this test as a measurement of general sympathetic activity, as approximately 50 % of the noradrenaline measured in an antecubital fossa vein is derived locally, mainly from muscle. Simultaneously, there is removal of incoming noradrenaline in the forearm which is not accounted for and consequently a given value may not be representative of the general sympathetic activity.[118] Arterial sampling reduces some of these problems.[119] Dihydroxyphenylglycol (DHPG) results from intraneuronal noradrenaline metabolism and is less dependent on local metabolism. We measured DHPG and noradrenaline in 8 patients with and without DAN and found that, whereas the supine plasma noradrenaline concentration alone could not differentiate the two groups, the ratio DHPG/noradrenaline almost completely differentiated the two groups.[120] Increments in plasma noradrenaline reflect increments in sympathetic activity, e.g. during standing or exercise. The presence of this response may differentiate patients with and without sympathetic neuropathy.[121] Theoretically, neuropeptide Y is a good peripheral measurement of sympathetic activity as there is no re-uptake after secretion. However, plasma neuropeptide Y does not decrease in patients with autonomic neuropathy.

Denervation Hypersensitivity

Another way to assess the autonomic nervous system is by measuring sensitivity to alpha- and beta-adrenergic receptor stimulation. The principle behind these tests is that the denervated end-organ shows hypersensitivity

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to infused neurotransmitters.[122] This is a well-known observation in idiopathic autonomic failure. We have investigated this phenomenon and the underlying pathophysiology in DAN.

Sensitivity to Infused Agonists

Patients with long duration diabetes with signs of diabetic peripheral somatic and autonomic neuropathy defined as abnormal vibratory perception threshold (VPT), decreased beat to beat variation in heart rate during deep breathing ($<$10 beats min^{-1}), and orthostatic hypotension (blood pressure fall of greater than 30 mmHg on standing) were studied. Patients had varying degrees of symptoms and signs of other late diabetic complications. Patients with long duration diabetes without any diabetic complications and healthy age-matched volunteers served as controls. Hilsted and colleagues investigated the metabolic, hormonal, and cardiovascular responses to graded infusions of adrenaline in these three groups of subjects.[123] Heart rate increase, blood pressure decrease, and increases in total peripheral vascular resistance, oxygen uptake, blood glucose, lactate and glycerol concentrations were significantly greater in patients with DAN compared to the other two groups. These results support the presence of a beta-adrenergic hypersensitivity in patients with DAN.

In a similarly designed study, we investigated the metabolic, cardiovascular, and hormonal responses to graded infusions of noradrenaline, a predominantly alpha-receptor agonist.[124] Patients with DAN showed a significantly greater increase in blood pressure (at a lower threshold), peripheral vascular resistance, and increments in glucose and beta-hydroxybuturate compared to the other two groups. No change in response to noradrenaline infusion was seen in cardiac output, other metabolites (lactate, glycerol) or hormones. We concluded that the hypersensitivity to alpha-adrenergic stimulation mainly involves the cardiovascular system and is primarily located in the resistance vessels in accordance with the findings of Bodmer.[125] Increased cardiovascular sensitivity to alpha-adrenergic stimulation has been demonstrated by others.[126,127] An exaggerated sensitivity to noradrenaline has been reported in Type 1 diabetic patients with microalbuminuria.[128] We could not demonstrate any correlation between albumin excretion rate and cardiovascular responses. However, due to the known coexistence of DAN and nephropathy, the original findings in patients with microalbuminuria may be explained by DAN in such patients. It is possible that DAN may play a pathogenetic role in nephropathy and hypertension often seen in long-term diabetic patients. Alpha-2 receptors have been shown to be responsible for the vasoconstriction seen in patients with microalbuminuria.[125] Our finding of an increased slope and the shift to the left in the dose–response curve is in agreement with true alpha-2 adrenoceptor hypersensitivity as a result of a baroreflex modulation and a postganglionic lesion.[129] This is in agreement with the findings in chronic autonomic failure.[130] Therefore denervation hypersensitivity is a characteristic of patients with DAN for both alpha- and beta-adrenoceptor stimulation.

Kinetics of Catecholamines

Hypersensitivity to alpha- and beta-adrenoreceptor agonists could be explained by altered kinetics including reduced metabolic clearance rates giving rise to increased plasma concentrations. This is substantiated by the finding that increased venoconstriction was found in DAN patients with noradrenaline but not with phenylepinephrine, which could indicate reduced neuronal re-uptake.[131] Furthermore, relatively high supine concentrations of plasma noradrenaline in DAN patients may be indicative of an altered clearance rate in these patients.

We measured these kinetic parameters using radiolabelled adrenaline in one study[132] and radiolabelled noradrenaline (neuronal re-uptake) and isoprenaline (no neuronal re-uptake) in another study.[133] In both studies we studied 8 diabetic patients with and without DAN. Adrenaline kinetics demonstrated that clearance was not significantly different between the two groups. However, the disappearance rate was increased and sojourn-time prolonged in patients with DAN. These findings may partly explain the increased responsiveness to adrenaline in these patients. An increased adrenaline secretion encountered in everyday situations like stress, hypoglycaemia, and exercise will as a result have a prolonged effect in these patients.

Noradrenaline kinetics revealed no differences between the two groups as regards disappearance rate or metabolic clearance rate of noradrenaline or isoprenaline. The appearance rate in plasma of noradrenaline was reduced in patients with DAN. A reduced basal plasma concentration and appearance rate of noradrenaline with identical clearance rates for noradrenaline and isoprenaline indicate a severe malfunction of the postganglionic sympathetic neurons. Neuronal inactivation appears not to be important for the inactivation of circulating noradrenaline in these patients. It is not clear, however, if the lowered appearance rate is due to a defect in storage, synthesis or release of noradrenaline in such patients. Furthermore, it could be due to denervation hypersensitivity in presynaptic receptors. Similar changes in kinetics of neurohumoral transmitters are seen in patients with idiopathic orthostatic neuropathy where a further decrease in clearance is observed.[134] Our data is in agreement with those of Hoeldtke *et al*.[135] but not with those of Esler and colleagues, who observed a decreased clearance of noradrenaline. This may be related to their use of venous blood sampling and a small number of patients in their study.[136]

Adrenergic Receptors

The kinetic data do not offer a full explanation of the reported denervation hypersensitivity in patients with

DAN. Increased numbers of adrenergic receptors found in patients with idiopathic autonomic failure may partly explain denervation hypersensitivity in such patients. Accordingly, we measured beta-2 adrenergic receptor densities and binding affinities, alpha-2 receptor densities, and isoprenaline stimulated cyclic AMP accumulation in mononuclear leucocytes in 8 diabetic patients with and without DAN and 8 healthy volunteers. We found no differences in any of these parameters between the groups.[137] There are several comments to be made in relation to these findings. Firstly, receptor density in peripheral blood cells may not necessarily reflect receptor density on target cells, although there is supportive evidence that it does *in vitro*.[138,139] Our data do not exclude the possibility of an increased adrenergic receptor density on target cells and an increased receptor number on fat cells has been demonstrated.[140] Further data on the receptor status at real target cells are needed. Secondly, in other studies a poor correlation has been demonstrated between clinical findings of haemodynamic sensitivity to catecholamines *in vivo* and the measurements of adrenoceptors.[138,139,141] We conclude that receptor measurement is a fallible index of the clinical denervation hypersensitivity syndrome. Thirdly, if our data reflect receptor status at target tissue, then they suggest that the mechanism behind denervation hypersensitivity lies distal to the adrenergic receptor and their linked adenylate cyclases. Altered catecholamine kinetics may also contribute as explained above.

Treatment

The treatment of DAN is most often symptomatic as no corrective therapy exists once damage has occurred. Several studies have looked at the beneficial effect(s) of near-normoglycaemia. Aldose reductase inhibition (ARI) has been studied.[63,142,143] All studies were secondary intervention trials, limited to evaluating the effect of ARI on abnormal cardiovascular response tests. The best results reported so far have been an arrest of deterioration in autonomic nerve function, and the clinical implication of such a finding is speculative.

Orthostatic Hypotension

Orthostatic hypotension is the most common and disabling symptom of DAN. The mechanisms that ensure maintenance of blood pressure in the standing position are complex and involve centripetal signals from baroreceptors with efferent sympathetic impulses to both the heart and peripheral blood vessels, i.e. resistance vessels and veins.

Treatment of orthostatic hypotension is often difficult, resulting in fluid retention and supine hypertension. Treatment involves non-pharmacological intervention with garments to increase venous return, supplementary salt intake to ensure water retention, headup tilt to correct nocturnal natriuresis, morning hypotension and reduce supine hypertension, recommendations to avoid sudden postural change, and large carbohydrate rich meals. Pharmacological measures that have been shown to be effective in clinical trials include fludrocortisone[144] (enhanced sodium retention and increased vascular resistance), metoclopramide,[145] indomethacin,[146] octreopide—a somatostatin analogue,[147] caffeine,[148] and midodrine.[149]

There have been anecdotal reports of a positive outcome with the beta-blocking agent pindolol in DAN.[150,151] The intrinsic sympathomimetic effect of this compound on denervation hypersensitivity, and its beta-blocking effect on vasodilatation, formed the rationale for this treatment. We have tested pindolol (15 mg day^{-1}) for 10 weeks in a randomized double-blind, placebo controlled, cross-over trial in 8 Type 1 diabetic patients with DAN and symptomatic orthostatic hypotension.[152] We could not demonstrate any effect on blood pressure, heart rate, or symptom scores. Our patients were less affected by DAN than the previously reported patients, who fainted upon standing. Low receptor occupancy has been argued as a prerequisite for the intrinsic sympathomimetic action to take place. However, patients with DAN may have normal or decreased numbers of receptors, and plasma noradrenaline concentrations may be normal. The diminished capacity for increased heart rate and blood pressure during exercise in patients with DAN, combined with our previous findings, could indicate an end-organ failure or a defect in post-receptor signalling in these patients which is not affected by pindolol. The use of beta-blocking agents in patients with diabetes may furthermore be accompanied by unwanted effects such as masking of hypoglycaemic symptoms, cardiac failure and/or impairment of peripheral circulation. Accordingly, beta-blocking agents cannot be advocated for use in the treatment of orthostatic hypotension in patients with DAN or at least only tried in the very severe cases.

Central Neuropathy

In contrast to the peripheral nervous system (PNS), the central nervous system (CNS) has only recently received attention as a potential target for late diabetic complications. In contrast to early impressions, the CNS is not protected from the complications of diabetes.[153] A number of vascular alterations in the brain are reported in diabetic patients, which include thickening of capillary basement membrane, alteration in cerebral blood flow and impaired autoregulation.[154,155] It is known that elderly patients with diabetes have a three-fold increase in risk of having an atherothrombotic brain infarction compared to their non-diabetic peers and hyperglycaemia may worsen the ischaemic brain damage.[153]

Neuropathological findings in the brain from Type 1 diabetic patients with microvascular complications demonstrate characteristic histological patterns of diffuse degenerative abnormalities with pseudocalcinosis, demyelinization, and atrophy.[156] Identical findings in peri-

pheral nerves are observed in patients affected by somatic neuropathy. These changes support the presence of a 'diabetic encephalopathy'.[157] As with peripheral nerve tissue the pathogenesis of diabetic encephalopathy is possibly related to either metabolic or vascular mechanisms or both. However, there are some differences between peripheral tissue and the brain. The ratio of the blood glucose concentration in brain and blood is increased in diabetes, and from animal studies it is known that Na/K-ATPase in CNS is increased but myo-inositol is not reduced. Reduced activity of aldose reductase in the brain is suggested, and advanced glycosylation endproducts are found in the brain. Further details are beyond the scope of this review: the reader is referred to the studies of McCall,[153] Bressel *et al*.,[155] and Mooridan.[158]

Electrophysiological Studies

EEG

Different electrophysiological methods have been applied to test nerve function in the central nervous system. Electroencephalograms (EEG), with recording of spontaneous cerebral activity, show specific abnormalities related to fluctuations in blood glucose. Hyperglycaemia together with ketoacidosis gives rises to the loss of alpha rhythm together with focal generalized theta–delta activity.[161] Hypoglycaemia *per se* results in decreased alpha activity and increased theta activity.[161] More non-specific changes have been demonstrated in long-term diabetic patients. In a study in children, EEG abnormalities were seen in up to 76 % and correlated to the degree of metabolic control and presence of diabetic retinopathy.[159] No valid data exist regarding EEG abnormalities in diabetic neuropathy.

Sensory Evoked Potentials

Sensory evoked potentials give more precise information on specific nerve function in the brain than EEG as they measure the impact of a specific sensory stimulus in a specific nerve in a more reproducible and sensitive manner. The most commonly used in diabetes research include the visual evoked response (VER), measuring the time of nervous impulse from the retina to the cortex, and the auditory brain stem response (ABR), measuring conduction along the acoustic nerve and the brain stem auditory pathways.

In 20 to 50 % of diabetic patients prolongation of nervous transmission (VER) is observed, with even newly diagnosed patients showing significant abnormalities.[159,160] Conflicting data exist as regards the relationship with other parameters of interest, e.g. duration of disease and metabolic control.[161] However, several studies have shown immediate improvement within a few days after the institution of strict metabolic control in patients previously in poor metabolic control.[102,162] Some investigators have demonstrated a positive correlation between abnormal VER and deteriorated peripheral nerve function[163] and other signs of late diabetic complications. Others have not been able to find such a relationship.[161,164] More studies addressing this specific question and the relationship between VER and the other signs of diabetic encephalopathy are needed to fully explain these findings of abnormal functioning of the ophthalmic nerve in diabetes mellitus.

We studied 20 diabetic patients with and 19 patients without signs of peripheral diabetic neuropathy.[165] Of the 20 patients with neuropathy, 14 (70 %) had signs of autonomic neuropathy, 8 (40 %) diabetic nephropathy, and 10 (50 %) proliferative retinopathy. ABR was performed in all patients and data obtained in 486 neurologically normal subjects without diabetes were used as the reference values. The results showed abnormal ABR with prolonged latency intervals in 40.0 % and 5.3 % of the patients with and without neuropathy, respectively. Cross correlation function was abnormal in 20.0 % of patients with neuropathy compared with only 5.3 % in those without neuropathy. When comparing the cumulative distribution of the latency intervals of both groups to the reference group, the difference was highly significant for both groups. Latencies were corrected for age, sex, and hearing thresholds and blood glucose levels were not different between the two groups when tested. As no deviation for the peripheral part of the nerve (J1) was found, we concluded that these findings could best be explained by the presence of neuropathy in the central part of the acoustic nerve. Several other studies have also shown abnormal ABR in diabetic patients.[163,166–170] In contrast to our conclusions, some have proposed the concomitant presence of a peripheral lesion.[168] Acute improvement in metabolic control does not seem to normalize abnormal ABR[170] and hypoglycaemia having only a minor influence on ABR.[171]

Neuroimaging

Another method of visualizing the central nervous system is by magnetic resonance scanning (MRS). Sixteen of the 20 diabetic patients of long duration with diabetic neuropathy (see section on Sensory Evoked Potentials 4.1.2) were investigated by this method (4 were excluded due to metallic clips in one of their extremities). A control group of 40 age- and sex-matched healthy volunteers without cerebrovascular risk factors were also tested.[165] We found abnormal signals in 69 % of the diabetic patients in contrast to 12 % of the controls. Diabetic patients with lesions were younger and had a higher number of lesions which were larger and more scattered compared to the control subjects. Our results were later confirmed[172] in a study of 10 patients with varying duration of diabetes and degree of late diabetic complications. In this study 70 % of diabetic patients had an abnormal MRS, compared to none in the control group. There was no demonstrable relationship between abnormal MRS and the duration of diabetes, the number of hypoglycaemic episodes and the presence of neuropathy, nephropathy or retinopathy. However, the number of

patients in this study was far too small to allow final conclusions. The abnormal signals detected could be due to an increase in the water content of the brain as a result of increased aldose reductase activity,[173] vascular ischaemia and/or structural changes in myelin in the brain's white matter. This condition, which is likewise characterized by axonal loss and demyelination with hyalinoid thickening of the walls of small arteries and multiple subcortical infarcts, is also known as subcortical arteriosclerotic encephalopathy or Binswanger's disease.[174] There is a need for further studies with MR scanning in diabetic patients in order to clarify the abnormalities seen.

Functional Tests

Auditory Test

Several studies have been performed to test hearing disorders in diabetic patients. Conflicting data exist, mainly due to heterogeneity of the patients examined. Also very few studies have addressed the question of whether impairment is related to microvascular complications elsewhere such as diabetic neuropathy. We investigated diabetic patients with and without late diabetic complications who were enrolled in the ABR study described above (see section on Neuroimaging). A well-defined sex- and age-matched non-diabetic population group was used as a control.[175] Patients with neuropathy showed a significant reduction in the hearing thresholds at the higher-frequency bands, compared with the other group of patients and control subjects. However, when adjusted for age, this difference was insignificant. Therefore, we could not demonstrate any differences between patients with or without diabetic neuropathy and the control group with respect to hearing thresholds. No correlation could be demonstrated between duration or severity of the diabetes and hearing thresholds. Our findings on hearing thresholds are in agreement with our findings showing no defect in the peripheral part of the acoustic nerve according to the ABR recordings. The results from our study agree with several other studies.[176] Some authors, however, have demonstrated a reduction in auditory thresholds in diabetic patients. In a study comparing newly diagnosed with long-duration diabetic patients,[177] there was no relationship between impaired auditory function and peripheral neuropathy but a positive correlation to duration of diabetes. It is difficult to make any firm conclusion based on the current literature but if hearing loss exists in diabetic patients due to diabetes, it is probably only minor. Only large scale studies in well-defined patients will be able to clarify this problem further.

Neuropsychological Test

The effect of diabetes on intellectual function has been addressed in several studies, often to investigate if hypoglycaemia has any deleterious effect. Acute hypoglycaemia is known to depress cognitive function at the time but the impact of recurrent hypoglycaemia on more long-term intellectual function is more controversial.[177] In the DCCT, an increase in hypoglycaemia was seen in the intensified controlled group compared to the conventionally treated patients. No difference was found in cognitive function between these two groups.[178]

The impact of hyperglycaemia or late diabetic complications, especially neuropathy, is seldomly addressed. In order to investigate if the findings of a central neuropathy as evidenced by ABR and MR scanning in patients with peripheral neuropathy had an impact on cognitive function we investigated the 20 previously described patients with peripheral neuropathy (see section on Sensory Evoked Potentials). A group of 120 healthy non-diabetic normal subjects served as controls. They all underwent neuropsychological examination including 17 tests of intelligence and cognition. Four measures of intelligence (DART reading test and three WAIS subtests) served as a basis for statistical correction of premorbid intelligence.[165] We found that diabetic patients with neuropathy scored below the expected normal values in most tests and significantly so in three (face recognition, picture arrangement, Wisconsin card sorting test). Most of our patients, however, had visual problems that could have influenced the outcome, although we did not detect any correlation between poor test performance and visual acuity or degree of retinopathy. Nevertheless, the seven tests that did not demand good visual acuity did not demonstrate any differences in neurophysiological behaviour between the patients and the controls. In a group of 48 diabetic patients with neuropathy, Lawson and colleagues likewise did not find any convincing neuropsychological deficits.[179] However, others have found a significant cognitive dysfunction in similar patients.[180,181] In a study of 142 Type 1 patients with long duration diabetes, peripheral polyneuropathy was the best predictor of impairment in cognitive function. Recent studies on the impact of diabetes *per se* on cognitive function are conflicting.[101,155,182] When assessing this problem it is important to adjust for confounding factors.

Based on histology, neurophysiology, neuroradiology, and neuropsychology there is a growing body of evidence for the existence of an affect on the central nervous system in patients with diabetes and peripheral diabetic neuropathy, i.e. diabetic encephalopathy. In addition there might be functional deficits, but they are mild and probably not sufficient to interfere with everyday life.

Summary and Future Aspects

Diabetic neuropathy is a frequent and disabling complication of diabetes. Due to the lack of a consensus relating to the definition and diagnostic criteria for diabetic neuropathy the incidence rate and prevalence data currently available are poorly described. Based on clinical measures, the incidence is approximately 50 % after 25 years of diabetes.

The pathogenesis is only partly understood but meta-

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bolic consequences of intraneural hyperglycaemia, glycosylation of neural proteins, altered and impaired blood flow, oxidative stress, autoimmunity and deprivation of nerve growth factors seem all to be involved to a greater or lesser extent. Symptoms are very variable but the most disabling ones involve pain, dysaesthesia, and orthostatic hypotension. Improved metabolic control postpones the onset and retards the progress of diabetic neuropathy. Only few pharmacological agents can offer symptomatic relief for this painful diabetic syndrome. We have shown that intravenous lignocaine (5 mg kg^{-1} body weight) and the oral lignocaine analogue mexiletine (10 mg kg^{-1} body weight) can significantly reduce symptoms of diabetic neuropathy. More research with compounds that affect the specific metabolic and vascular derangement known in this disease is much needed.

In autonomic failure, orthostatic hypotension is the most disabling symptom. Beta-blocking agents with intrinsic sympathomimetic activity have been recommended, based on anecdotal observations. We could not demonstrate any effect of the beta-blocking agent pindolol in a double-blind, cross-over trial.

We have shown that diabetic patients with autonomic failure have denervation hypersensitivity both to alpha- and beta-adrenoceptor stimulation. From our kinetic experiments we can conclude that part of the reason for this enhanced response is an increased disappearance rate and prolonged sojourn-time of infused adrenaline. The appearance rate in plasma of noradrenaline was also found to be reduced, however, metabolic clearance rate of both neurotransmitters was not altered. Furthermore, we could not demonstrate any increased numbers of adrenergic receptors on circulating platelets, nor differences with regard to cyclic AMP production after agonist stimulation. Although platelets are not the real target cells, our findings suggest that a more profound post-receptor signalling defect could be responsible for the denervation hypersensitivity observed in these patients. This needs to be further clarified.

In an attempt to determine the existence of a central nervous system neuropathy we investigated a group of diabetic patients with and without neuropathy assessing auditory brain responses and carrying out magnetic resonance brain scanning and neuropsychological tests. We observed that patients with diabetic neuropathy had abnormalities in both magnetic resonance brain scanning and central abnormalities in auditory brain responses. However, neuropsychological testing only revealed minor functional defects. Further research is needed to better clarify these abnormalities in the brain, their classification, and their relationship to other established microvascular complications of diabetes.

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